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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/114,844	07/14/98	ASHKENAZI	A 1129R1

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EXAMINER	
KAUFMAN, C	
ART UNIT	**PAPER NUMBER**
1646	22

DATE MAILED: 07/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/114,844	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- Th MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,29,34,35 and 38-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,29,34,35 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,7* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *20* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The preliminary amendment of May 2, 2001, has been entered.

Claim Objections

Claim 40 and its dependent claims are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Since claims 1 and 6 are drawn to polypeptides and claim 40 is drawn to a nucleic acid, the dependent claim could be infringed by something that does not infringe the base claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-10, 13-14, 29, 34, 35, 40-41, 45-48, 58 and dependent claims 11-14, 38, 42-44, 49-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 are indefinite because the metes and bounds cannot be determined. It is not clear what range is intended by "at least about ...%".

Claim 1 is indefinite because it is unclear what is meant by the term "modulates" apoptosis.

Claims 1, 6 and 41 are indefinite because it is unclear what property distinct from the sequence set forth in the claims the term "native sequence" is intended to impart.

Claim 6 is indefinite because section be is drawn to "fragments", and it is unclear if the fragments must be consecutive as well as what their physical relationship in the isolated extracellular domain sequence is one to another. The claim is additionally indefinite because not

only is it unclear if all fragments must retain the same biological activity of a native sequence of RTD polypeptide.

Claims 4 and 6-9 are drawn to sequences, which is indefinite. Proteins or nucleic acids should be claimed, but not their sequences. A sequence is not a product, it is a property of a product.

Claim 10 and dependent claims are indefinite because a polypeptide is fused to a sequence. This rejection could be obviated by, for example, stating that the polypeptide is fused to a heterologous protein.

Claims 13 and 14 are indefinite because it is unclear if the "immunoglobulin sequence" means a full-length Ig sequence or can be a fragment, such as constant region.

Claims 29 and 34 is indefinite because it is unclear if "the RTD polypeptide of ... claim 6" is referring to the ECD or the polypeptide described in (a).

Claims 34 and 35 are indefinite because a composition must comprise more than one component. It is unclear what the composition includes besides the RTD polypeptide, and it is unclear if the RTD polypeptide is an active ingredient of the composition or merely present in trace amounts. Knowing whether the RTD polypeptide is critical to the composition is necessary to understand the breadth of the claim. If the polypeptide is the active ingredient, this rejection could be obviated by adding to the end of the claim a phrase such as, "and a diluent". Note that in Claim 35, the inclusion of instructions does not affect the composition.

Claim 40 is indefinite because a nucleic acid cannot comprise a sequence. It can be represented by a sequence or have the sequence set forth in SEQ ID NO:X. This also leads to confusion regarding the "nucleotide sequence ... encodes the "extracellular domain sequence"- instead of a extracellular domain itself. This rejection could be obviated by phrasing such as: An isolated nucleic acid comprising a polynucleotide encoding the RTD polypeptide of claim 1 or the extracellular domain of claim 6 [once the "sequence" confusion in claim 6 is resolved--see above]. Dependent claim 40 could be similarly clarified by then stating: wherein said polynucleotide encodes....

Claims 45-47 are indefinite because a cell cannot comprise a cell. The rejection could be obviated by using phrasing such as, "which is [comprises] a CHO cell."

Claims 48 and 58 is confusing because of the term "using" and because culturing the host cell does not necessarily lead to production of the polypeptide. This claim resembles a "use" claim. If a method of production is being claimed and the host cell produces the polypeptide, it is suggested that wording such as the following be used: A process for producing an RTD polypeptide, comprising culturing the host cell of claim 54, wherein said nucleic acid comprised by said vector is expressed to produce the RTD polypeptide of claim 1 or 6.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6, 40 and 42-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide at least 95% identical to SEQ ID NO:1, wherein said polypeptide binds Apo-2 ligand or inhibits the ability of Apo-2 ligand to induce apoptosis, or an ECD of RTD polypeptide which comprising a single fragment of SEQ ID NO: 1, wherein the fragment binds Apo-2 ligand or inhibits the ability of Apo-2 ligand to induce apoptosis, does not reasonably provide enablement for stimulatory functions of the polypeptide or fragment(s). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 6 includes a sequence comprising fragments that retain at least one biological activity of a native sequence of RTD polypeptide. On page 17, lines 17-23, of the specification, "biological activity" is defined broadly, including stimulating or inhibiting the apoptosis. Claim 1 requires the claimed polypeptide to "modulate" apoptosis. Claim 40 is a dependent claim drawn to a nucleic acid encoding the polypeptide of claim 1 or 6. The examples in the specification using the full-length RTD polypeptide or a fusion of the extracellular domain (ECD) with a portion of human IgG show that the ECD of RTD binds Apo-2 ligand but does not transmit a signal. This is unlike DR4 and DR5 which when either binds Apo-2 ligand, apoptosis

is stimulated. Therefore, the only biological activity taught by example in the specification and for which there is guidance for how to use is that of inhibition or blocking of apoptosis or apoptotic signaling. There is no other direction on how to use the polypeptide to otherwise "modulate" apoptosis.

Further, it is shown in the specification that RTD has the following sequence identities with the ECD of functionally related prior art proteins: DR4-55%, DR%-56%, DcR1-67%. The identities with the intracellular domain of those proteins is similar (p. 623, lines 11-17). Because there is nothing known about the structure-function relationship of RTD beside the fact that residues 1-212 bind Apo-2 ligand, and because half of the amino acids in RTD differ from the next closest known related receptors, one skilled in the art would know which amino acids could be changed to retain the function possessed by the unaltered RTD ECD, which is inhibition or blocking of apoptosis or apoptotic signaling. A polypeptide that is 80% or 90% identical to SEQ ID NO:1 may have 39-77 amino acids that are different from SEQ ID NO:1. The mature ECD is only 156 amino acids long. Changing 39 represents an alteration of more than 20% of those amino acids. This gives great scope to the claimed polypeptide for which the instant specification cannot support and for which the prior art cannot substitute in this case. Additionally, there is no guidance or example in the specification to allow the skilled artisan to know what would need to be altered in order to make a polypeptide that functions differently than the full RTD ECD. These reasons for lack of enablement commensurate in scope with the invention as claimed pertain to the nucleic acid encoding as well. If one cannot use the protein, then one cannot use the nucleic acid encoding it. If the nucleic acid does not encoding a protein which can be used or is not identical to a portion of the nucleic acid which encodes the RTD polypeptide in nature so that it could be used as a specific probe, then one skilled in the art would not know how to use it.

Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an ECD comprising amino acids 56-212, does not reasonably provide enablement for an ECD comprising fewer than those amino acids (*e.g.*, 99-139 and/or 141-180). The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims are drawn and "extracellular domain sequence of RTD polypeptide" comprising 99-139 or 99-139 with 141-180. The specification says these two regions are cysteine-rich domains. There is no showing in the specification or prior art that these regions are sufficient for Apo-2 ligand binding. While these regions may be necessary for ligand binding, if they alone are not sufficient, one skilled in the art would not know what to do with a polypeptide comprising these regions that could not bind a ligand. For the RTD polypeptide and related polypeptides DR4 and 5, it has been shown that the full (mature) ECD can bind a ligand; however, there is not showing that less than the full ECD can bind. As far as the prior art, the skill in the art is low and the state of the art has little to contribute to details of Apo-2 ligand receptor function/structure relationship other than of major features such as the full polypeptide and ECD. As a result, it would require undue experimentation to use the claimed sequence (or ECD) which does not comprise at least the complete mature ECD (amino acids 56-221 of SEQ ID NO:1) of the RTD polypeptide.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-6, 8-14, 29, 38-45, 47-55, 57 and 58 are rejected under 35 U.S.C. 102(e) as being anticipated by Ni et al. (US Patent 6,124,580).

Ni et al. teach TR10, a TRAIL-binding protein for which SEQ ID NO:2 is identical to SEQ ID NO:1 of the instant application. Also taught is the extracellular domain (amino acids 56-210) expressed as a fusion protein with human IgG Fc that bound TRAIL (Example 5). Nucleic acids encoding and vector and host cell comprising the nucleic acids are also taught, including a construct with amino acids 56-386 of the protein (col. 36, lines 38-41) fused to an FLAG-epitope tag. Host cells and vectors comprising the nucleic acid are taught in Examples 1

and 3B. Although E. coli host cells were not actually produced, they could have been immediately envisioned by one of ordinary skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14, 29, 34, 35 and 38-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ni et al. (US Patent 6,124,580) as relied upon above and for the additional teachings set forth below.

Ni et al. also teaches the ability to produce the protein by expressing a vector comprising the encoding nucleic acid in yeast and other host cells (col. 14, lines 12-41). Also, that the extracellular domain is from about amino acid 56-212 of FIGS. 1A-F (amino acids 1-157 of SEQ ID NO:2) of the patent (col. 8, lines 52-56). It is suggested that TR10 or the ligand binding domain thereof be in a composition with a carrier suitable for injection for antibody production or potential therapeutic use (e.g., col. 24, lines 52-59, and col. 26, lines 29-66)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to express the full-length receptor or a soluble TRAIL-binding fragment thereof in yeast or other host cells to optimize activity of the expressed protein as well as efficiency and cost of production, as was well known in the art at the time the invention was made. It also would have been obvious to use an extracellular domain of amino acids 56-212 instead of 56-210 in the constructs previous described for protein purification or ligand binding assays since Ni et al. say that the full extracellular domain extends to amino acid 212. It would have been obvious to have the TR10 protein or the ECD thereof in a container for transport or isolation, for example, prior to use in a Western Blot (e.g., col. 35, lines 6-7), as was routine in the art.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Rauch et al. (US Patent 6,072,047) teach a receptor called TRAIL-R that binds TRAIL (Apo-2 ligand) but has a sequence distinct from that of the instant application.

Name Usage

It is noted that other names for RTD that appear in the art are TR10, DcR2, TRAIL-4 and Tango-74.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

July 10, 2001